disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides; and n is an integer from 0 to about 6. Oligomers comprising these compounds are useful for modulating the synthesis of proteins.

REMARKS

Applicants confirm the election of Group II, Claims 9-10, with traverse. Claims 1-8 and 11-14 are cancelled without prejudice to their presentation in a divisional or continuation of this application. Claims 9 and 10 have been amended and new claims 15 and 16, dependent from claim 9 added. The definition of the T groups has been modified in accordance with the specification to clarify that the pending claims are drawn to oligomers.

Claims 9-10 have been rejected under 35 U.S.C. § 101. The specification and Claims 9-10 have been objected to under 35 U.S.C. § 112. Claims 9-10 have been rejected under 35 U.S.C. § 103.

At page 3, paragraph 4 of the Examiner's office action, the Examiner stated that the title of the invention is not descriptive and that a new title is required. The title has been amended to more accurately indicate the invention to which the claims are directed.

At page 3, paragraph 5 of the Examiner's office action, the Examiner objected to the Abstract of the Disclosure. Applicants submit an amended Abstract. Applicants believe the Abstract, as amended, accurately describes, "the general nature of the compounds of the invention and their use" and, as such is proper.

At page 4, paragraph 2 of the office action, the Examiner objected to the specification because of a number of informalities. The Examiner stated that the chemical structures throughout the specification are too faint to be interpreted unambiguously. Other minor matters were also pointed out.

Applicants submit replacement pages 3-11 and 15 with clear chemical structures. No new matter has been added by these substitutions.

Applicants have inserted the subscript "2" for the 2-amino group of the 2-amino-adenosine derivative on replacement pages 7, 9 and 15. These replacement pages do not introduce any new matter and are merely corrections of chemical structures whereby the "2" of NH_2 was inadvertently omitted. Applicants have also rewritten claim 10 to reflect the insertion of the subscript "2".

At page 4, paragraph 3 of the office action, Claims 9-10 were rejected under 35 U.S.C. § 101 because the invention allegedly lacked patentable utility. The Examiner stated that these claims "encompass numerous varieties of chemical groups that have no size limits". The Examiner also stated that "such large and bulky substituents, some possessing charged amino groups, would predictably create both stearic and charged interactions that would interfere with and even prevent the requisite hybridization with a complimentary strand."

Further, the specification and claims 9-10 were objected to under 35 U.S.C. § 112, first paragraph, for allegedly failing to provide an adequate written description and failing to adequately teach how to make and/or use the invention.

Hybridization dynamics are well understood by those skilled in the art. In fact, Example 49 of the present specification teaches methods of analyzing hybridization fidelity of oligomers of the present invention. One skilled in the art

would appreciate that the length or size of the such groups must, of course, follow the general "wisdom" pertaining to steric interference and charge interactions which may affect hybridization fidelity. Thus, such limitation is inherent in the specification and does not negate the utility or enablement of the present invention.

Whether or not one could "load up" a substituient X with bulky functions in a determined effort to defeat the goals and purposed of the invention is not the point. One of ordinary skill in the art will know to avoid a level of bulkiness inconsistent with the teachings and objects of the present invention and with good scientific practice. Moreover, such person is told how to monitor doing so. Such person will have no difficulty in following the practices set forth specifically in the specification without undue experimentation. There can be no real question that Applicants have placed the invention into the hands of the public. The contrary view relies upon speculation. Accordingly, Applicants respectfully request withdrawal of these rejections and objections.

At page 7, paragraph 3 of the Examiner's Office Action, Claims 9-10 were rejected under 35 U.S.C. § 112, first paragraph. The Examiner stated that the terms "intercalating agent", "reporter molecule", "polyamines", "polyamides", "polyalkylene glycols" and "polyethers" are inadequately supported. Applicants respectfully traverse this rejection.

The terms "intercalating agent", "reporter molecule", "polyamines", "polyamides", "polyalkylene glycols" and "polyethers" are well known to those skilled in the art. "Intercalating agents" are molecules that insert themselves between neighboring bases of an oligonucleotide (see page 18, bottom paragraph), an example of which is acridine. "Reporter molecules" are molecules which may aid in the identification of

another molecule either visually or otherwise (see page 18, bottom paragraph). Two examples of reporter molecules are biotin and various fluorophores, both of which are disclosed in the specification. The terms "polyamines", "polyamides", "polyalkylene glycols" and "polyethers" are very well known to those skilled in the art as being polymers of amines, amides, alkylene glycols and ethers respectively, and as such do not require further definition. Accordingly, Applicants respectfully request withdrawal of this rejection.

Claims 9-10 were rejected under 35 U.S.C. § 112, second paragraph. The Examiner stated that claim 10 was rendered indefinite because the subscript "2" was missing from the 2-amino group of the purine ring. Claim 10 has been amended to include the omitted subscript.

It was further alleged that Claims 9-10 were rendered indefinite by the phrase "a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides" because the functional language did not readily permit the person of ordinary skill in the art to understand and recognize clearly the metes and bounds of the invention.

Pharmacodynamic properties include oligonucleotide uptake, oligonucleotide resistance to degradation and/or strengthened sequence-specific hybridization with RNA (see bottom of page 18 to top of page 19). Groups of compounds that improve these properties are alkyl chains, polyamines, ethylene glycols, polyamides, aminoalkyl chains and amphipathic moieties (see top of page 19). Pharmacokinetic properties include oligonucleotide uptake, distribution, metabolism or excretion (see top of page 19). Applicants submit that the "functional language" more accurately describes the groups of compounds than the chemical nomenclature and that one skilled in the art would know the

"metes and bounds" of the invention as disclosed by said language.

Claims 9-10 were also alleged to be indefinite because of the phrase "T3 and T5 independently are OH or a further subunit of said oligomer that is joined to said structure". The Examiner states that it is not clear that this definition rules out both T3 and T5 being hydroxyls at the same time. Claims 9-10 were also alleged to be indefinite because the points of attachment of T3 and T5 to the oligonucleotides were allegedly not specified. The Examiner stated that T3 should connect to the 3'-terminal phosphate and that T5 should connect to the 5'-terminal of an oligonucleotide. Applicants respectfully traverse this rejection.

Claims 9-10, as amended, rule out the possibility of both T_3 and T_5 being OH groups. Furthermore, one having ordinary skill in the art would understand the linkage of the claimed bases to other bases. To further aid in this understanding, the linkage groups have been termed T_3 (for 3'-linkage) and T_5 (for 5'-linkage). Applicants respectfully request withdrawal of this rejection.

At page 10, paragraph 2 of the Examiner's Office Action, Claim 9 was rejected under 35 U.S.C. §103 as being unpatentable over Iribarren *et al.* in view of Iribarren *et al.* [sic, Cotten *et al.*]. The Examiner states that Cotten *et al.* discloses oligomers comprising at least one 2'-O-modified guanosine nucleotide. The Examiner also states that Iribarren *et al.* teaches that an allyl group is also an effective 2'-O-substituent in an oligonucleotide. The Examiner concludes that the substitution of a halogen atom such as fluorine at the distal carbon of an alkyl group would not be expected to alter significantly the properties of said alkyl group. The Examiner further states that the substitution of a 3'-fluoropropyl group

for either the 2'-O-methyl or the 2'-O-ethyl of Cotten *et al.* or the 2'-O-allyl of Iribarren *et al.* is well within the ability of the person of ordinary skill in the art at the time of the invention. Applicants respectfully traverse this rejection.

There is no teaching or suggestion by Cotten *et al.* to further modify the 2'-O-methyl or 2'-O-ethyl oligoribonucleotides by the addition of further carbon groups as well as an additional halide to the guanine nucleotide. Further, Irribarren *et al.* teaches away from further modifications of 2'-O-allyl. At page 7750, column 2, Irribarren *et al.* states that,

> "further attempts to prepare alkylated RNA probes that are superior to the 2'-O-allyl oligoribonucleotides should concentrate on either four-carbon or alternative three-carbon groups."

Thus, neither Cotten *et al.* nor Iribarren *et al.*, alone or in combination teach the oligomers of Applicants' invention.

Claim 10 was rejected under 35 U.S.C. § 103 as being unpatentable over Cotten *et al.* in view of Iribarren *et al.* and Sproat *et al.* The Examiner states that Cotten *et al.* and Iribarren *et al.* make obvious an oligomer with at least one adenosine nucleoside possessing a 2'-O-alkyl group and cites Fig. 1 of Cotten *et al.* The Examiner also states that Sproat *et al.* teaches the substitution of 2-aminoadenosine for adenosine in antisense oligomers. The Examiner concludes that an oligomer with at least one 2'-O-modified 2-aminoadenosine would also have been obvious to the person of ordinary skill in the art to enhance the affinity of the oligomer to its complimentary sequence. Applicants respectfully traverse this rejection. As argued above, the combination of Cotten *et al.* and Irribaren, *et al.* is critically flawed in that, *inter alia*, Irribaren teaches away from the present invention.

Sproat *et al.* does not satisfy the deficiencies of this combination. There is no teaching or suggestion by Sproat *et al.* to modify the 2'-aminoadenosine compound. Furthermore, there is no teaching or suggestion in Sproat *et al.* of long chain 2'-O- substitutions as provided by the present invention. The 2'-O-allyl compound depicted as compound V in Fig. 1 is simply a reaction intermediate for the preparation of the 2'-O-allylguanosine compound. There is no teaching or suggestion to further modify compound V of Sproat *et al.* to produce the Applicants' invention. However, in an effort to facilitate prosecution of the present application, Applicants have amended Claim 10 to require that R_1 be C_4 to C_{20} alkenyl. Thus, neither Cotten *et al.*, Iribarren *et al.* nor Sproat *et al.*, alone or combined teach the Applicants' invention as disclosed in the amended claims.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and allowance of all pending claims. Early favorable notification to that effect is earnestly solicited.

Respectfully submitted,

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